

AIR OXIDATION OF α -TERPINEOL

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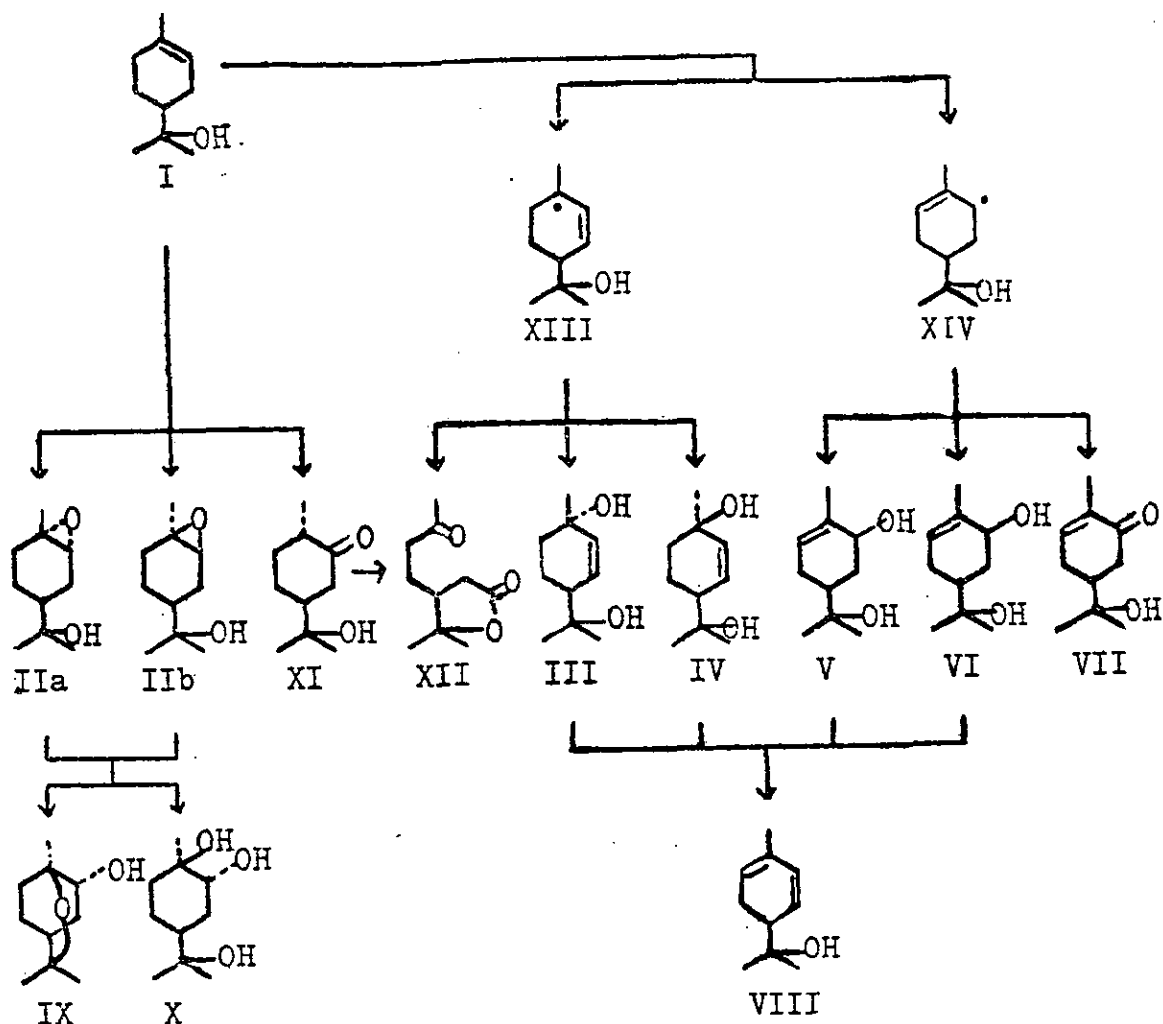
Oxidation of α -terpineol by atmospheric air resulted twelve products, which seemed more complicated than the results of the previous works. All the products were identified and rationalized. The mechanisms of some minor reactions were discussed.

It is known that certain terpenes and their derivatives are oxidized by contacting them with a gas rich in oxygen such as air. During the process of isolation and purification of essential oils of *Libocedrus Formosana* Florin¹⁾, it was noticed that carvacrol and *p*-menthane-1 α , 2 β , 4 β -triol might be artifacts produced by autoxidation of 4-terpineol²⁾. These results prompted us to undertake air oxidation of a similar compound, α -terpineol(I). We describe below the results of this investigation.

Atmospheric air was pumped to flow through α -terpineol at 80°C for 24 hrs. The reaction mixture was then separated by various chromatographic methods. The products obtained and their relative percentages as the peak areas shown by GLC with polyethyleneglycol column were as follows: α - and β -8-hydroxycarvomenthene-1, 2-oxide (IIa and IIb) (1.7%), *trans*-1, 8-dihydroxymenth-2-ene(III) (7%), *cis*-1, 8-dihydroxymenth-2-ene(IV) (8%), *trans*-sobrerol(V) (15%), *cis*-sobrerol(VI) (7%), 8-hydroxycarvotanacetone (VII) (30%), 8-hydroxy-*p*-cymene (VIII) (1%), 2 α -hydroxy-1, 8-cineole (IX) (7%), *p*-menthane-1 β , 2 α , 8-triol(X) (18%), 8-hydroxycarvomenthone(XI) (0.8%), and homoterpenyl methyl ketone(XII) (2%).

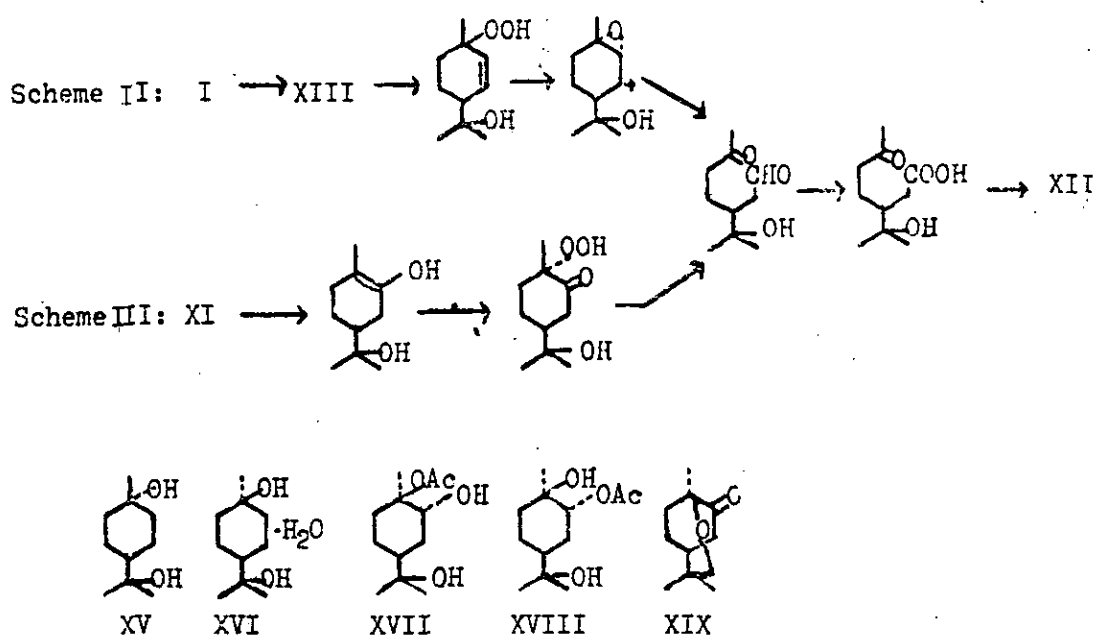
Compounds V and VIII were identified by comparison with authentic samples. Oxidation of α -terpineol with SeO₂ gave VII, which when reduced with LiAlH₄ gave V and VI. Catalytic hydrogenation of III and IV gave *cis*-*p*-menthane-1, 8-diol(XV) and terpinol(XVI), respectively, which were then identified by comparison with authentic samples. Hydroboration³⁾ of α -terpineol followed by chromic acid oxidation gave XI. Permanganate-periodate oxidation⁴⁾ of α -terpineol gave XII. Epoxidation of α -terpineol followed by distillation in vacuo gave the epoxide mixture (IIa, IIb). This epoxide mixture, when treated with buffered acetic acid⁵⁾, gave two compounds: IX(35.6%), which came from IIa with 1 β -acetoxy-*p*-menthane-2 α , 8-diol(XVII) as an intermediate, and 2 α -acetoxy-*p*-menthane-1 β , 8-diol(XVIII) (21%), which came from IIb. Saponification of XVIII gave X.

This experiment indicated that air oxidation of α -terpineol led to a more complex mixture of compounds than the work of J. P. Bain *et al.*⁶⁾. The main features



(scheme I) of this air oxidation can be explained by the " α -methylene mechanism" as described by G. Ohloff *et al*¹⁰ in his study of autoxidation of some monoterpenes. In an attempt to determine the mode of formation of IX and X, α -terpineol was oxidized in two other conditions, first with particular caution to avoid moisture and second with carbon dioxide removed from air. The temperature and flow rate were unchanged. In both cases the oxidation products contained no X and only a small amount of IX, while the amount of epoxide mixture (IIa, IIb) increased proportionally. Thus the formation of IX and X were rationalized in terms of acid catalysed opening of the epoxides, though IX might also be a by-product in the formation of epoxide (IIa, IIb). The carbon dioxide and moisture in the air are responsible for the formation of weak acid, which is yet sufficiently acidic to enact acid sensitive reactions. In order to get a further proof, the epoxides was oxidized by air. When in the presence of one drop of pure water, 65% of X and a minor amount of IX were formed, but no reaction was assured in the absence of water or carbon dioxide.

Though the α -methylene mechanism may satisfactorily explain the formation of



XII (scheme II)¹⁰, the other source of which is from XI (which, being only a minor product, may be a by-product in the formation of epoxide) by scheme III¹¹ catalyzed by weak acid. To further confirm this, we oxidized XI with air. In the presence of moisture 30% of XI was transformed to XII at 80°C after 24 hrs.

From the results in this experiment and our observation of previous works¹⁰, we have noticed that the time consuming process of isolation of natural products damages the reality of components to a considerable extent. The existence of some of the compounds in plants is therefore questionable.

EXPERIMENTAL

The α -terpineol used was supplied by Tokyo Kasei Kogyo Co. Ltd. with d_4^{20} 0.937, n_D^{20} 1.482, $[\alpha]_D^{20}$ -13.1 ($c=5$, ethanol). I. R. spectra were determined with Perkin Elmer Model 700 apparatus. N. M. R. spectra were determined with Varian Model T-60 apparatus. G. L. C. were carried out with Varian Aerograph Model 705, 1200 and 90-P apparatuses. All m. ps. were uncorrected.

Air Oxidation of α -Terpineol in the Presence of Moisture

The atmospheric air was pumped to flow through 5.18 g of α -terpineol at 80°C with a flow rate of 120 ml/min for 24 hrs without avoiding moisture. G. L. C. showed 60% of the reactant was oxidized. The products were chromatographed on silica gel column (65 g., acetone-washed) into eight fractions. Fraction I was eluted by *n*-hexane, fraction II by *n*-hexane/ benzene 95:5, fraction III by *n*-hexane/benzene 4:1, fraction IV-VI by *n*-hexane/benzene 1:1, fraction VII by pure benzene, and fraction

VIII by methanol. The main component of fraction I and II was unreacted α -terpineol. Fraction III was 2 α -hydroxy-1, 8-cineole(IX) (61.5 mg), with m. p. 64.5-66°C, ν_{\max} 3400 cm^{-1} , $\tau(CCl_4)$ 9.00 (s, Me), 8.89 (s, Me), 8.80 (s, Me), 7.27 (OH), 6.43 (dd, J=10 Hz, 4 Hz, HCOH). Fraction IV was purified by G.L.C. to give 8-hydroxy-*p*-cymene (VIII), with ν_{\max} 3350, 1600, 1500 cm^{-1} , $\tau(CCl_4)$ 8.57 (s, 2 Me), 7.70 (s, Me), 2.92 (d, J=8Hz, 2 H), 2.64(d, J=8 Hz, 2 H). Fraction V was separated by preparative G.L.C. to give three compounds: trace of epoxide(IIa, IIb), ν_{\max} 3400, 1260, 1150, 930, 855, 835, 780, 760 cm^{-1} ; trace of 8-hydroxycarvomenthone(XI), ν_{\max} 3400, 1705, 1160 cm^{-1} ; and 8-hydroxycarvotanacetone(VII) (131 mg), ν_{\max} 3400, 1660 cm^{-1} , $\tau(CDCl_3)$ 8.78 (s, 2 Me), 8.23(bs, Me), 7.67 (OH), 3.29(bs, $W_{1/2}$ =10 Hz, vinyl H), λ_{\max}^{EtOH} 236 nm(ϵ =10600). Fraction VI was 144 mg of compound VII. Fraction VII was purified by G.L.C. to give a small amount of homoterpenyl methyl ketone(XII), with ν_{\max} 1760, 1705 cm^{-1} . Fraction VIII was dissolved in water and extracted with ether. The ether layer was separated by preparative G.L.C. to give four compounds: *cis*-1, 8-dihydroxymenth-2-ene(IV) (55 mg), m. p. 84.5-85.5°C, ν_{\max} 3350, 1650 cm^{-1} , $\tau(CDCl_3)$ 8.84 (s, Me), 8.80 (s, Me), 8.73 (s, Me), 7.83 (2 OH), 4.31, 4.12 (1 H each, d, J=12Hz, H-C=C-H) *trans*-1, 8-dihydroxymenth-2-ene(III) (53 mg), m. p. 118-119.5°C, ν_{\max} 3350, 1650 cm^{-1} , $\tau(CDCl_3)$ 8.80 (s, Me), 8.74 (s, Me), 8.72 (s, Me), 7.52 (2 OH), 4.20, 4.00 (1 H each, d, J=12z, H-C=C-H), *trans*-sobrerol(V) (72 mg), m. p. 148.5-149.5°C, ν_{\max} 3300 cm^{-1} , $\tau(CDCl_3)$ 8.78 (s, 2 Me), 8.22 (s, Me), 5.96 (bs, HCOH), 4.36 (bs, vinyl H); *cis*-sobrerol(VI) (40 mg), ν_{\max} 3400 cm^{-1} , $\tau(CDCl_3)$ 8.80 (s, 2 Me), 8.09 (s, Me), 5.92 (m, HCOH), 4.47 (m, vinyl H). The aqueous layer was purified by G.L.C. to give *p*-menthane-1 β , 2 α , 8-triol(X) (110 mg), m. p. 105.5-107°C, ν_{\max} (KBr) 3370 cm^{-1} , τ (Acetone- D_6) 8.88 (s, 2Me), 8.81 (s, Me), 7.03 (3 OH), 6.39 (bs, $W_{1/2}$ =7 Hz, HCOH).

Air Oxidation of α -Terpineol in the Absence of Moisture

The experimental set was the same as the moist air oxidation but in this case air was dried by $CaCl_2$ before flowing through the reactant. After 24 hrs the crude products were shown by G.L.C. to have the same component peaks as the previous experiment except the absence of compound X and the presence of one epoxide peak, which was then obtained by preparative G.L.C. with IR spectrum coinciding with that in the moist air oxidation products and $\tau(CCl_4)$ 8.89 (s, 2Me), 8.72 (s, Me), 7.17 (bs, $W_{1/2}$ =3 Hz, epoxide proton of IIa) (27.3%), 7.05 (bs, $W_{1/2}$ =4.8 Hz, epoxide proton of IIb) (72.7%). Besides, the peak of compound IX decreased to 2%.

Air Oxidation of α -Terpineol in the Absence of CO_2

The carbon dioxide was removed from air by passing through saturated NaOH solution in advance. The other conditions are the same as the previous moist air oxidation. G.L.C. of the crude product showed similar peaks to that of the dry air oxidation product.

Air Oxidation of 8-Hydroxycarvomenthone(XI)

Atmospheric air was pumped to flow through 1.0 g of XI with a rate of 180 ml/min at 80°C for 24 hrs. Preparative G.L.C. gave 70% unreacted ketone and 30% homo-terpenyl methyl ketone(XII) with I.R. spectrum coinciding with that of the air oxidation product of α -terpineol and τ (CDCl₃) 8.72(s, Me), 8.55(s, Me), 7.84(s, --COCH₃). Prolonged reaction, however, seemed to improve the yield very little.

8-Hydroxycarvomenthene-1,2-oxide(IIa, IIb) from α -Terpineol

α -Terpineol 15.7 g was shaken with 0.130 mole of freshly prepared perbenzoic acid at -5°C for 1 hr, then maintained at 0°C for 22 hrs. The solution was then extracted with 5% NaOH solution to remove the benzoic acid formed. 17 g of epoxide mixture was obtained, with I.R. and N.M.R. similar to that of the air oxidation product of α -terpineol, but the percentages of the signals of the two epoxide protons changed to 37.9% of IIa and 62.1% of IIb. A small amount of IX (5%) was also obtained as a by-product.

J. P. Bain *et al* has reported⁹ that the two stereoisomeric epoxides, IIa and IIb can easily be separated by distillation in vacuo. In our work, however, they were inseparable either by distillation or by G.L.C. The intention to separate them by chemical methods failed and we assigned τ 7.17 to IIa and τ 7.05 to IIb only tentatively. The I.R. data of IX and epoxide mixture were similar to that of α - and β -epoxide described in J. P. Bain's work, respectively, but chromic acid oxidation of IX gave 2-keto-1,8-cineole(XIX), thus further confirmed our assertion.

Air-Catalysed Hydrolysis of the Epoxide(IIa, IIb)

Dry air was pumped to flow at a rate of 185 ml/min through the mixture of 1 drop pure water and the epoxide (3.45 g) at 80°C for 12 hrs. Preparative G.L.C. gave 65% of *p*-menthane-1 β ,2 α ,8-triol(X) and a minor amount of IX. The same experiment without the addition of water or with CO₂ excluded from air left all the reactant unreacted. The prolonged resting of the mixture of epoxide and water open to the atmosphere at room temperature for several months also resulted no identifiable chemical reaction.

2 α -Hydroxy-1,8-cineole(IX) and *p*-Menthane-1 β ,2 α ,8-triol from Epoxide(IIa, IIb)

The epoxide (4g) was treated with 4 g of anhydrous sodium acetate in 25 ml of acetic acid at 55-60°C for 3 hrs¹⁰, then extracted with ether. Preparative G.L.C. gave 35.6% of IX with m.p. 64-66°C, I.R. and N.M.R. spectra identical with that of the air oxidation product of α -terpineol. Another compound obtained was 2 α -acetoxy-*p*-menthane-1 β ,8-diol(XVIII) (21%), with ν_{\max} 3400, 1715 cm⁻¹, τ (CDCl₃) 8.81(s, 3 Me), 7.91(s, -OCOMe), 8.23(s, 2 OH), 5.08(t, J=3.8 Hz, HCOAc) When saponified with dilute NaOH, this acetate gave the triol X, with m.p. 106-107°C, I.R. and N.M.R. spectra identical with that of the air oxidation product of α -terpineol.

8-Hydroxycarvotanacetone(VII) from SeO_2 Oxidation of α -Terpineol

α -Terpineol 15.4 g was treated with SeO_2 , 18.6 g at 60°C for 2 hrs. Column chromatography on silica gel (100 g) gave 80% of VII, with I.R. and N.M.R. spectra identical with that of the air oxidation product of α -terpineol.

***trans*- and *cis*-Sobrerol(V and VI) from 8-Hydroxycarvotanacetone**

LiAlH_4 , 27.5 mg in 20 ml of dry ether was added dropwise into 0.42 g of VII obtained from SeO_2 oxidation of α -terpineol. Preparative G.L.C. gave 10% of *trans*-sobrerol and 65% of *cis*-sobrerol, with their physical data identical with that of the air oxidation products of α -terpineol.

Hydrogenation of *trans*- and *cis*- 1, 8-Dihydroxymenth-2-ene(III, IV)

Catalytic hydrogenation of 30.8 mg III in isopropyl alcohol using Pd-C as catalyst resulted *cis*-*p*-menthane-1, 8-diol(XV) with m. p. 154.5 - 156°C , ν_{max} 3350, 1130 cm^{-1} , $\tau(\text{Acetone-D}_6)$ 8.87(s, 2Me), 8.83(s, Me), 7.05(2OH). By the same way, 28.5 mg of IV gave terpinol(XVI), with m.p. 119 - 120°C , ν_{max} 3100-3400 (broad), 1180, 1140 cm^{-1} . The physical data of these two hydrogenation products are both identical with that of authentic samples.

8-Hydroxycarvomenthone(XI) from α -Terpineol³⁾

α -Terpineol 10 g and NaBH_4 , 2.5 g were both dissolved in 60 ml of T.H.F. in stirring and 11.34 g of BF_3 -etherate was added in a period of 1 hr. The solution was then maintained stirring at 25°C for one day. The solution of 10 g CrO_3 in 40 ml of water and 8 ml of concentrated H_2SO_4 was then added dropwise in 15 minutes. When extracted with ether and chromatographed on neutral silica gel, 70% of XI was obtained with I.R. spectrum identical with that of the air oxidation product of α -terpineol. N.M.R. spectrum showed: $\tau(\text{CCl}_4)$ 9.03(d, $J=6$ Hz, Me), 8.85(s, 2 Me), 6.53(OH); $\tau(\text{Benzene})$, 9.00(d, $J=6$ Hz, Me), 8.85(s, 2 Me), 7.2(OH). The small difference between $\tau(\text{CCl}_4)$ and $\tau(\text{Benzene})$ suggests the equatorial methyl group.

Homoterpenyl methyl ketone(XII) from α -Terpineol⁴⁾

α -Terpineol 0.4 g, 200 ml of 5% *t*-butanol aqueous solution containing 0.69 g of K_2CO_3 , and the stock solution containing 10.7 g of NaIO_4 and 0.20 g of KMnO_4 were mixed together and stirred for 45.5 hrs at room temperature. The product, when separated with column chromatography, gave 55% of unreacted ketone and 40% of XII, with I.R. spectrum identical with that of the air oxidation product of α -terpineol and $\tau(\text{CDCl}_3)$ 8.72(s, Me), 8.55(s, Me), 7.84(s, $-\text{COCH}_3$).

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